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# Virulence-Associated Factors of Mycobacterium leprae in Innate Immune Recognition and Evasion

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**Abstract**
The bacterium M.leprae is an obligate intracellular species. The skin and peripheral nerves are primarily affected by this pathogen. The Schwann cells in peripheral nerves and the dermal histiocytes (tissue macrophages) are the primary targets for this bacteria.The first sign of indeterminate leprosy is often single or multiple, hypopigmented, or somewhat erythematous macules with thermal sensation loss .The illness has been classically described along a Th1/Th2 spectrum, where the Th1 pole represents the most restricted presentations and the Th2 pole the most disseminated ones. Both innate and acquired immune responses are involved . M. leprae infected keratinocytes secrete various cytokines and chemokines and induce highly effective immune responses. People who have poor cell immune responses to the bacillus also have robust humoral immune reactions and high serum antibody levels, which complicates their ability to halt the transmission of M. leprae. However, current data indicate that local innate immune responses are essential in determining the disease's various clinical presentations. The immunoregulatory function of innate immune molecules and their interaction with the nervous system, which can impact homeostasis and lead to the onset of inflammatory episodes throughout the course of the illness, are best studied using leprosy as a model. These observations offer therapeutic intervention targets for modulating innate immune responses in people against microbial illness.

**Key worlds:**Mycobacterium leprae, Leprosy, Innate Immune Response, Th1 / Th2, Schwann Cell.

## 1.Introduction

Leprosy is regarded as one of the earliest infectious diseases ever known to mankind . Leprosy primarily affects peripheral nerves, skin, mucosal membranes, and eyes(Ansari et al., 2025).

Leprosy is a chronic infectious disease that mainly affects the skin and the peripheral nerves. *Mycobacterium leprae*, an obligate intracellular pathogen with tropism for macrophages and Schwann cells, is the causative agent of the disease. Recently, Mycobacterium lepromatosis, a bacterium phylogenetically very close to *M. leprae*, was identified as the causative agent of diffuse lepromatous leprosy with Lucio's phenomenon(Cabral et al., 2022).

*M. leprae* has a unique predilection to infect non-myelinating and myelinating Schwann cells, the enwrapping glia of the peripheral nervous system. Once intracellular, this pathogen provokes multiple alterations in Schwann cells, affecting both early and late cellular events, including modifications in the glucose and lipid metabolism and trafficking, myelin dismantling and lipid droplet accumulation, neurotrophin secretion, and changes in gene expression, leading to Schwann cell reprogramming to an immature, highly proliferative phenotype(de Oliveira Brügger et al., 2023).

Infection of peripheral nerves by M. leprae is a hallmark of leprous neuropathy, causing sensory, motor, and autonomic disability, thus making it one of the most common causes of peripheral neuropathy worldwide(Orujyan et al., 2022).

Transmission from person to person is thought to be through the aerosol route, mainly in persons living in close contact for extended periods of time. Therefore, daily and continuous exposure with untreated patients make household contacts (HHC) a high-risk group in disease control strategies(Bouth et al., 2023). Together with the difficulties in the clinical diagnosis of leprosy and the absence of laboratory tools, drug resistance is an aggravating factor in controlling leprosy(Bouth et al., 2023).

Regarding the clinical, bacilloscopic, histological and immunological presentation, the Ridley-Jopling classification of leprosy has been divided into five types related to the order of increasing severity: tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL), and lepromatous (LL). In this sense, the clinical spectrum of the disease can be summarized in a variation of severity between the Tuberculoid and Lepromatous poles, being separated by Borderline forms in the middle. People who have weak cell immune responses against the bacillus also have strong humoral immune reactions and large levels of serum antibodies, which makes it difficult for them to control the spread of M. leprae. While LL is characterized by robust humoral immunity, TT is linked with strong cellular immunity, poor humoral immunity, and granulomatous local skin lesions(Marcos Jessé Abrahão Silva et al., 2024).

Susceptibility is also influenced by inherited traits, with variable expression of several genes related to the immune response, showing a correlation between the expression of some genes and certain presentations. Of particular relevance, in lepromatous leprosy and in type 2 leprosy reaction, genes involved in the humoral immune response are expressed at high levels, in particular genes for immunoglobulin receptors or for proteins of the classical complement pathway; in contrast, genes linked to the cell immune response are intensely expressed in the paucibacillary and reverse reaction forms(Junior et al., 2022).

This article briefly reviews the clinical features as well as the immunopathological mechanisms related to the establishment of the different polar forms of leprosy, the mechanisms related to M. leprae–host cell interactions and prophylaxis and diagnosis of this complex disease. Host genetic factors are summarized and the impact of the development of interventions that prevent, reverse or limit leprosy-related nerve impairments are discussed(Pinheiro et al., 2011).

## 2. Overview of Innate Immune Recognition in Leprosy

Leprosy continues to be a major health issue worldwide since it is curable but not preventable. This complicated illness is defined by two interconnected characteristics. First, affected people experience a vast array of cell-mediated immunological responses as a result of a chronic mycobacterial infection. Secondly, because to the infection and following immunological processes, it causes peripheral neuropathy(Kimta et al., 2024).

From an immunological standpoint, leprosy occurs in a range of manifestations. The lepromatous pole (LL) is distinguished by mostly humoral immune responses and high bacterial burdens, whereas the tuberculoid pole (TT) is distinguished by strong cellular immune responses and low bacillary loads. Between these extremes are borderline forms (BT, BB, and BL), which exhibit intermediate immunological, histological, and clinical traits. In multibacillary forms (BB to LL), the large bacillary load promotes a strong antibody response, but these antibodies do not prevent bacterial proliferation(Froes Junior et al., 2025).

In the long-term history of leprosy, leprosy reactions are acute, immunologically driven episodes that lead to major functional morbidity. With a reported lifetime prevalence of close to 50% among leprosy sufferers, these may happen before, during, or after multidrug therapy (MDT) is finished(Mehta et al., 2025).

Two primary groups may be made for leprosy reactions (LRs). Reactions to type IV leprosy, often known as "reversal" reactions, are categorized as such. allergic reaction. The above-mentioned response is typically seen in people who have been BL was identified in him. This state is defined by a targeted cellular immune response. specifically directed against the M. leprae bacterium's antigens(Dewi et al., 2023).

The pathogenesis of T2R involves type III hypersensitivity due to inadequate clearance of antigen-antibody complexes, resulting in inflammation and leukocyte chemotaxis. Skin biopsies of ENL patients show complement and immunoglobulin deposition in the dermis, similar to an Arthus reaction(Mehta et al., 2025).

It is well known that the generation of proinflammatory cytokines is necessary for a strong response against M. leprae in the nasal mucosa and skin, and that T cell-mediated immunity is essential in the pathogenesis of leprosyT cells with central memory (TCM) and effector memory T cells (TEM) are the two categories of memory T cells. Compared to TCM cells, which have modest or no effector function but have a greater proliferative capacity and may quickly proliferate and differentiate into effector cells upon reactivation, TEM cells demonstrate immediate effector function. TH1, TH2, TH17, TH9, TH22, and Tregs are just a few of the many distinct subsets into which TEM cells can be separated(Cabral et al., 2022).

### 2.1Role of Macrophages

In the development of leprosy, macrophages (Mfs) play a crucial role. To control innate and adaptive immunity and maintain homeostasis in response to the emergence of inflammatory events during the disease, bone marrow-derived monocytes differentiate into macrophages (Mfs). However, the immunological roles of Mφs are strongly influenced by particular signals from antigen-specific immune cells and the environment in which they are located(Quaresma et al., 2023).

M. leprae is well-known for parasitizing selectively non-professional phagocytic cells such as MHC class II negative Schwann cells and for having an affinity for immunologically privileged sites, such as the peripheral nerves, which enables it to live in the mammalian host. A mechanism controlled by Jagged 1 (JAG1), a protein present in the vascular endothelium, has recently been shown to cause endothelial cells to induce monocytes to differentiate into M1 macrophages when activated with interferon-gamma (IFN-), and to become M2 macrophages when endothelial cells are not stimulated(Pathak et al., 2025). Proinflammatory cytokines, such as IFN-gamma, cause M1 macrophages to become active. IL-4 and IL-13 stimulate M2 macrophages, which are involved in tissue restoration and fibrosis and have anti-inflammatory effects. Leprosy research recently recognized and examined the relationship between M4 macrophages and atherosclerosis. Markers for M4 macrophages, such as CD68, S100A8, and MMP7, were shown to have higher numbers in LL lesions than in TT lesions when immunolabeled. Low CD163 expression levels may have inhibited the phagocytosis of M4 macrophages. The prevalence of M4 macrophages, which are linked to atherosclerosis, may have an impact on foam cell formation, pointing to the beginning of an oxidative stress response. This encourages the synthesis of chemokines and the recruitment of monocytes. An adaptive process involves the appearance of Virchow cells(Sugawara-Mikami et al., 2022).

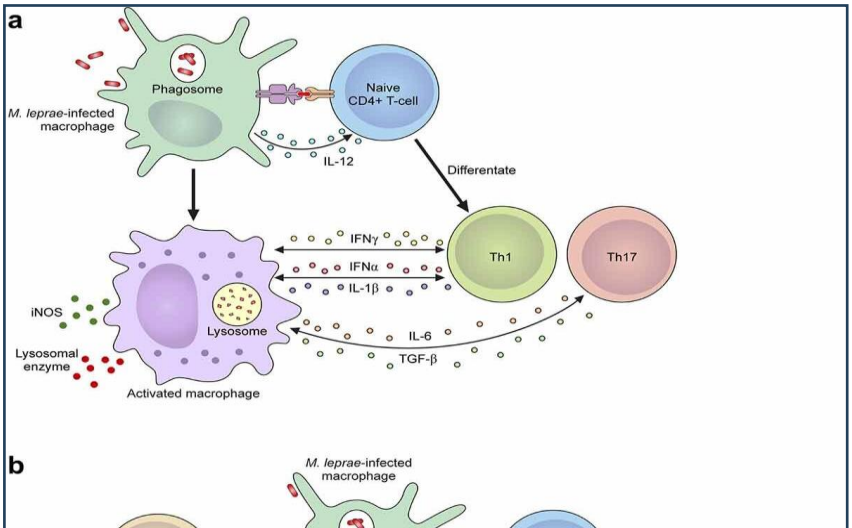

**Figure 1:** The leprosy response's mechanism. (a) A cellular immune response generated by CD4+ T cells drives T1 R. Tissue damage is caused by the release of pro-inflammatory Th1 cytokines such as IFN-, TNF-, IL-1, IL-6, IL-2, IL-12, TGF-, and iNOS from activated macrophages. (b) ENL is a widespread proinflammatory response with neutrophil infiltration. Additionally, it's possible to see the lesions and circulation's complement activation, immune complexes, higher CD4+/CD8+ T cell subset ratios, and elevated levels of inflammatory cytokines like TNF-. Low cellular immunity is seen with ENL, although there are enough B cells and plasma cells to create antibodies against M. leprae. Numerous neutrophilic infiltrations are seen during the acute phase of ENL lesions. Apoptosis of the cells is caused by the cytotoxic granule proteins, such as granzymes and perforin, that an activated CD8+ T cell releases(Sugawara-Mikami et al., 2022).

### 2.2 Dendritic Cells, Antigen Presentation, and Cross-Talk with Adaptive Immunity

Because dendritic cells (DCs) are professional antigen-presenting cells that recognize and react to hazard signals and then begin and control effector T-cell responses, they bridge the gap between innate and adaptive immunity(Clarkson et al., 2012).

DCs have a remarkable capacity to sample their environment, capture and process exogenous antigens into peptides, which are subsequently loaded onto major histocompatibility complex class I molecules for presentation to CD8+ T cells. This mechanism, known as cross-presentation, is crucial for starting and controlling CD8+ T cell responses to intracellular pathogens and tumors(Moussion & Delamarre, 2024).

The IL-1 family and IL-6, which are proinflammatory cytokines, facilitate the recruitment of immune cells for effective defense. Significantly, following Mtb infection or Ag uptake, mature DCs travel to the draining lymph nodes (dLNs) and encourage T cell recognition of the pathogen, which causes T cell polarization in the various microenvironments of infection sites(Kim & Shin, 2022).

### 2.3 Schwann Cells as Immunologically Active Cells

Neurodermatological features from M. leprae infection in human Schwann cells are sometimes challenging to identify(Jesus et al., 2022). The lipid-rich matrix, which is primarily made up of mycolic acids, makes up the cell wall of M. leprae, and phenolic glycolipid I (PGL-I) stands out as a crucial virulence factor. Through interaction with CR1, CR3, and CR4 receptors, PGL-I facilitates bacillary absorption by macrophages. It also attaches to specific targets, like α-dystroglycan on Schwann cells, causing myelin sheath injury and the formation of nerve lesions(Froes et al., 2025). Immunofluorescence in nerve biopsies identified TNF, TNF receptors, and TNF-converting enzymes in Schwann cells. Additionally, the production of transmembrane TNF and TNF receptor 1 was increased by *Mycobacterium leprae* infection of Schwann cells. In addition, TNF boosted the release of interleukin-6 and interleukin-8, but *Mycobacterium leprae* caused the release of interleukin-23. *Mycobacterium leprae* made Schwann cells more sensitive to TNF, which caused inflammation mediated by TNF and localized demyelination, which in turn caused nerve damage in leprous neuropathy(Calderone et al., 2024). Evolutionary analysis shows that M. leprae experienced a large drop in gene content in tandem with its adaptation to exclusively infect human cells, particularly Schwann cells and macrophages. Nearly half of its genome was lost as a result of this genetic decay, although genes connected to lipid anabolism, glucose anabolism and catabolism, and energy metabolism were spared. The loss of genes necessary for growth utilizing lipids as the only carbon source is thought to be the cause of *M. leprae's* reliance on host glucose intermediates for survival(Medeiros et al., 2016).

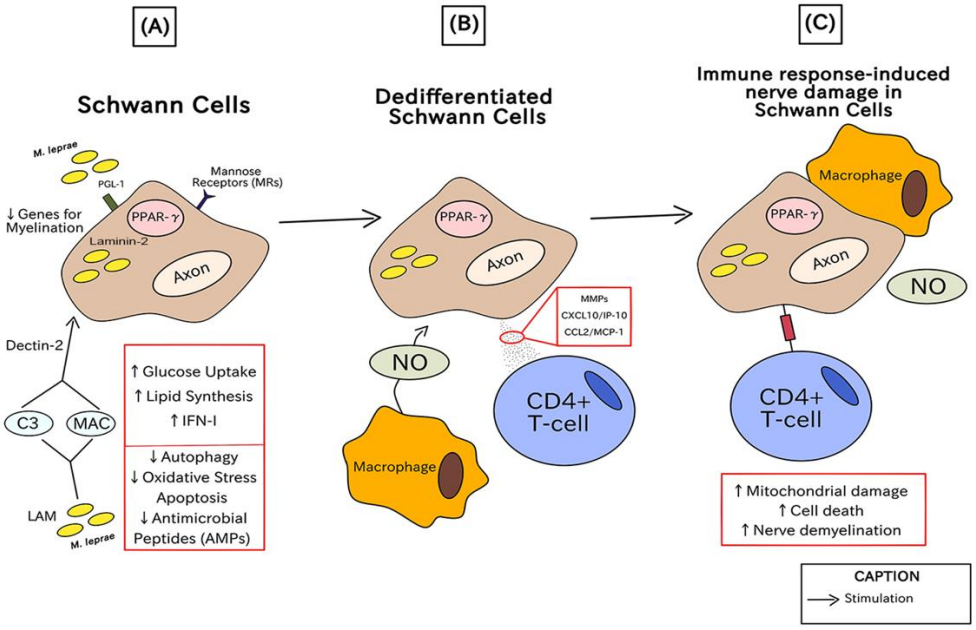


**Figure 2:** Damage to the Schwann cells is how leprosy affects the human nerves(Marcos Jessé Abrahão Silva et al., 2024).

Schwann cells, the glial cells of the peripheral nervous system (PNS), are uniquely able to create the myelin sheath surrounding axons and supply trophic chemicals for neuronal survival. Terminally differentiated adult Schwann cells display unprecedented plasticity despite having a complex differentiation/myelination program during development; they can turn off the myelin program and reach a dedifferentiated state. ML exploit the plasticity of adult Schwann cells to colonize and create a bacterial niche within this privileged and protected niche once invaded, as the blood-nerve barrier limits immune cell movement within the PNS(Masaki et al., 2014).

### 3 Mechanisms of Innate Immune Evasion

Ridley-Jopling classified leprosy into five categories based on clinical features, histopathology, and immunological processes: Tuberculoid (TT), Borderline tuberculoid (BT), Borderline (BB), Borderline lepromatous (BL), and Lepromatous (LL). BT and TT are distinguished by a low bacterial burden, little infection, a strong Th1 immune response, and the synthesis of pro-inflammatory cytokines, in particular. LL and BL are distinguished by a high bacterial load, a strong Th2 immunological response, the release of anti-inflammatory cytokines, and a dispersed infection (Jiang et al., 2024).

IFN-activation causes a number of pathways to improve the antimicrobial capabilities of macrophages so that they can kill intracellular infections like Mtb and M. leprae. Among the key antibacterial mechanisms include phagolysosomal maturation, ROS/RNS production, autophagy/LAP, and improved antigen presentation. Macrophages produce NO, a potent antibacterial molecule, by iNOS/NOS2 expression after being stimulated with IFN-. It is important to manage mycobacterial infections since they interfere with the structure and metabolic functions of bacterial cells. IFN- increases the microbicidal activity of macrophages by increasing enzymes that promote ROS production (Imran et al., 2025).

It is hard for people who have weak cellular immunological reactions to the bacillus to halt the dissemination of M. leprae since they also have potent humoral immune reactions and significant levels of serum antibodies. In contrast to LL, which is defined by strong humoral immunity, inadequate humoral immunity, and granulomatous skin lesions in the region, TT is linked to robust cellular immunity (Marcos Jessé Abrahão Silva et al., 2024).

The tuberculoid (T) pole of leprosy is distinguished by a robust cellularly mediated immunological response against M. leprae. The lepromatous (L) leprosy types, which happen in extremely sensitive individuals with a low cell immune response to the pathogen and a high bacterial load that is seen as the primary source of infection, are found at the opposite pole. Forms that exist somewhere between the two extremes are considered borderline (Vidal et al., 2025).

### 3.1 Inhibition of Phagosome–Lysosome Fusion

Intracellular multiplication is possible for all pathogenic mycobacteria. However, there is growth in phagosomes of macrophages. They have different mechanisms for surviving inside the cell. It varies greatly from one disease-causing species to the next (Frehel & Rastogi, 1987).

In an in vitro study utilizing Mycobacterium bovis Bacille Calmette-Guérin (M. bovis BCG), the tryptophan aspartate-containing coat protein (TACO), a crucial host protein, was found to be critical for the survival of bacilli within macrophages and the inhibition of phagosome-lysosome fusion (Suzuki et al., 2006).

For the release of inflammatory mediators and the triggering of suitable cell activation, the receptors that participate in the development of the phagolysosome are necessary. It has also been demonstrated that pathogens develop tactics to hinder P-L fusion. They might leave the phagosome, interfere with the host's defense mechanism by preventing phagosome ripening, and live and reproduce there (Carranza & Chavez-Galan, 2019).

*Mycobacterium microti* (vole tubercle bacillus), Toxoplasma gondii, and Legionella pneumophila are a few of the microorganisms. We wanted to further understand the process through which mycobacteria prevent fusion, so we set out to do the following: (a) ascertain whether consuming live *M. microti* would cause stasis of periphagosomal lysosomes, similar to what is observed in healthy monolayers treated with chemical inhibitors; (b) if so, contrast it with the lysosome motions following phagocytosis of a fusiogenic mycobacterium like *M. lepraemurium*; and (c) determine whether an M. microti-induced lysosome stasis might impair the fusion of lysosomes with separate phagosomes of a distinct fusiogenic organism (e.g., Saccharomyces cerevisiae) ingested by the same cell afterward (Hart et al., 1987).

The promiscuity between communicating components and the large number of fusion proteins lead to the mechanistic redundancy of this crucial phagocyte activity. Due to the plethora of fusion proteins and possible binding partners, it is expected that the spatiotemporal organizations, regulatory signals, and roles of the fusion machinery in PL fusion are still not fully understood. We highlight the advancements made in the area of phagocyte biology in this article since these gaps in the literature are still active study fields (Nguyen & Yates, 2021).

### 3.2 Modulation of Cytokine Profiles

Cytokines, small glycoprotein molecules that are essential to the immunopathology of leprosy, mediate cell-to-cell communication in the immune system (Pitta et al., 2023).

The leprosy condition may be divided into two main groups: multibacillary (MB) and paucibacillary (PB). Cytokines are crucial for triggering host-pathogen interactions and immunopathogenesis in leprosy. The Th1 (IL-2, IL-12, TNF-, IFN-) cytokine response, local infection, and robust cell-mediated immune response are linked to the onset of the disease in PB form, whereas the MB form is linked to a Th2 and Th3 cytokine (IL-10, TGF-, IL-4) response, localized skin lesions, considerable antibody production, and a very low CMI response (Tarique et al., 2020).

IL-12 stimulation causes IFN- to be released by natural killer (NK) cells and T helper 1 (Th1) cells, which also undergo Th1 differentiation. IFN- acts as an antimycobacterial immune response by stimulating macrophages. TNF-α has the capacity to activate macrophages, in addition to other pro-inflammatory actions. A counter-regulatory cytokine, IL-10 has been shown to have an impact on the immunomodulatory effects of IL-12. IL-10 is generated during bacterial infection and has been demonstrated to promote the formation of Th2 immunity and inhibit the production of inflammatory mediators(Kang et al., 2004).

Monocytes/macrophages were the primary producers of IL-10, which was released from the PBMC of healthy donors and patients following stimulation with M. leprae. By stimulating PBMCs in the presence of neutralizing anti-IL-10 mAb, it was discovered that endogenous IL-10 production inhibits PBMC proliferation and the release of TNF-alpha, GM-CSF, and IFN-gamma. Contradictory findings from studies utilizing neutralizing anti-IL-4 mAb showed that leprous patients showed the greatest improvement in PBMC proliferative responses as a consequence of internal IL-4 generation(Sieling et al., 1993).

### 3.3 Manipulation of Macrophage Polarization

According to studies, leprosy skin lesions exhibit distinct macrophage polarization, with the M1 phenotype being more common in TT patients' granulomas and the M2 phenotype being visible in LL granulomas (Marin et al., 2021). In vitro, IL-4 causes M2 polarization, while LPS and IFN-gamma cause M1 polarization. M1 macrophages are primarily responsible for the immune response against tumor and pathogenic bacteria. Conversely, M2 macrophages aid in tissue regeneration, help fight parasitic infections, and are primarily involved in the-inflammatory process (Zhang et al., 2025). M is capable of phenotypically altering and expressing co-stimulatory molecules like cytokines and receptors, which are necessary for the development of effective immunological responses. IFN-γ activation causes Mφs to undergo classical activation, which results in the production of MφM1, which has excellent pathogen-killing properties and

stimulates the production of pro-inflammatory cytokines such as IL-6, IL-12, inducible nitric oxide synthase (iNOS), and TNF-α(Quaresma et al., 2023) .Macrophages are thought to be one of the principal sources of MCP-1/CCL2. Acute neuritis and the start of the infection may both be indicated by demyelinating patterns in NCS. MCP-1/CCL2 levels were high in PNL patients and significantly linked to demyelinating patterns in NCS(Pitta et al., 2023).

Along with these two types of immune response, a recent study has identified the presence of Th9 immune response in leprosy. In its PB form, IL-9 has a proinflammatory effect because it inhibits the activity of IL-10. The IL-9 expression in the MB form has a distinct feature in that it might inhibit the synthesis of IL-4, IFN-, and TNF. IL-10 promotes an immunomodulatory response in this sort of reaction(de Carvalho et al., 2024). The TLR4 SNP, which facilitates early detection, is a sign of vulnerability. Moreover, the investigations discovered *M. leprae* DNA in biological samples from asymptomatic contacts who developed the disease after a two-year follow-up period(Pereira de Oliveira et al., 2024). Patients with leprosy may have acute inflammatory episodes during the disease's clinical progression called reversal reactions (RR) or erythema nodosum leprosum (ENL). RR is characterized by an elevated cell-mediated immune response, along with activation of CD4+ T cells and macrophages, as well as an increased expression of pro-inflammatory mediators. It was shown that patients receiving HAART are more likely to develop RR(da Silva et al., 2020).

### 3.4 Interference with TLR Signaling

Besides acting as a physical barrier, respiratory epithelium cells create a variety of pattern recognition receptors (PRRs), like Toll-like (TLRs), RIG-1-like, and NOD-like receptors, which recognize pathogen-associated molecular patterns (PAMPs), triggering a local innate immune response and organizing a subsequent adaptive immune response to fight the infection. The recognition of PAMPs stimulates the Jak-Stat, NF-B, and IRFs signaling pathways, which in turn causes the creation of cytokines, chemokines, reactive oxygen and nitrogen species, and antimicrobial peptides, all of which contribute to the early containment of infection by prompting the recruitment of immune cells and a crucial immunological response(Dias et al., 2021). The functional expression of pattern recognition receptors, such as Toll-like receptors (TLRs), allows epithelial cells to activate innate immune cells like macrophages and dendritic cells (DCs). Chemokines are one way that epithelial cells proactively regulate the local immune response and direct mucosal DCs to promote B lymphocyte IgA class switching(van Hooij & Geluk, 2021). In addition, TLR signaling promotes the expression of antibacterial peptides (AMPs) and other proteins that immediately kill microorganisms. The high number of TLRs in immunological cells (macrophages, dendritic cells, neutrophils, mast cells, and natural killer (NK) cells), as well as in epithelial and endothelial cells, triggers the innate immune system and creates a suitable, specialized response. As a consequence, the detection and elimination of pathogens becomes more challenging in the absence of TLR signaling. Nevertheless, unmanaged TLR signaling results in chronic inflammation and tissue damage, as demonstrated by severe systemic inflammation and sepsis. Microbial proteases act as virulence factors and are key modulators of TLR signaling, with targets within and outside host cells(Ciaston et al., 2022).

### 3.5 Evasion within Schwann Cells

The enwrapping glia of the peripheral neurological system, myelinating and non-myelinating Schwann cells, are specifically susceptible to infection by *M. leprae*. When this pathogen enters the cell, it causes several alterations in Schwann cells, including changes in glucose and lipid metabolism and trafficking, which affects early and late cellular events(Brügger et al., 2023).

While *M. leprae* is recognized to cause Schwann cell dedifferentiation, the mechanisms through which this process leads to nerve damage are still poorly understood(Girardi et al., 2023).

The two main cell types that are most frequently attacked by this bacteria are histiocytes (tissue macrophages) of the skin and Schwann cells of the peripheral nerves, which are important for carrying nerve impulses. As reddish infiltration or as whitish papules or rashes, skin lesions emerge.(M. J. A. Silva et al., 2024).

Intracellular *M. leprae* may be present in peripheral nerve SCs in leprosy sufferers. Despite the extensive study into the interactions between *M. leprae* and SCs, the precise methods are still unknown and the findings may even be at odds. According to a fascinating study, *M. leprae* may transform adult SCs into a progenitor/stem cell-like state with mesenchymal characteristics by lowering genes involved in SC differentiation and raising genes mostly involved in mesoderm development(Ma et al., 2023).

Once this pathogen is inside cells, it causes numerous changes in Schwann cells, interfering with both early and late cellular events, such as alterations in glucose and lipid metabolism and trafficking. Neuropathy is a chronic, multifaceted disorder caused by a number of factors that impact Schwann cells and the nerve's other non-neuronal cells. Because there is no gold-standard rodent model that resembles human leprosy neuropathy, research on Schwann cells in leprosy is based mostly on in vitro and in vivo (human biopsies) analysis. New discoveries have been made in the last ten years concerning what occurs to Schwann cells following exposure to leprosy bacilli (either alive or dead) or its antigens. Thus, a review of these Schwann cell-centered processes and their possible consequences on nerve pathology's development is necessary to provide an understanding of how this complicated glia-pathogen interaction may cause or underlie the illness (Brügger et al., 2023).

## 4. Host Genetic Factors Influencing Innate Recognition

Susceptibility to leprosy is greatly impacted by human genetic variables, and over 30 genomic loci have been connected to leprosy phenotypes. The most strongly leprosy-associated genetic variations were identified through genome-wide association studies (GWAS) as single nucleotide polymorphisms (SNPs) within the Major Histocompatibility Complex (MHC) on chromosome 6p21(Dallmann-Sauer et al., 2020).

The outcomes of the infection may be influenced by genetic variables and the immunological condition of the host. A strong immune response and a small number of microorganisms (tuberculoid or paucibacillary) to a weaker immune response and a bigger burden of organisms (lepromatous or multibacillary) are the two extremes of leprosy, making it an excellent paradigm for researching the genetic foundations and immunological responses of chronic illnesses(Long et al., 2021).

The usage of molecular techniques used to determine single nucleotide polymorphism (SNP) of Toll-like receptors (TLRs), especially TLR1, TLR2, and TLR4, have been shown to be correlated with unique leprosy clinical symptoms. The correlation between TLR SNPs and susceptibility to leprosy, as well as the immunological profile of leprosy patients, has already been studied. While TLR1 and TLR4 SNP were linked to differential production of chemokines and cytokines, TLR2 SNP was related with an increased risk of leprosy, according to studies (Cunha et al., 2023).

The highest amounts of LRs are primarily displayed by cells of the myeloid lineage, including monocytes, macrophages, and dendritic cells, although they are expressed by many different types of solid tissue cells and leukocytes(Santana et al., 2017).

According to human genetic research, differences in TLRs affect how vulnerable people are to several illnesses. We showed earlier this month that a microsatellite polymorphism in TLR2 was strongly linked to the manifestation of reversal reaction in leprosy patients. However, neither leprosy type nor leprosy susceptibility itself were significantly affected by this polymorphism. Thus, we assumed that polymorphisms in TLRs other than TLR2 may affect the illness's susceptibility(Bochud et al., 2009).

The capacity of immunological cells to eliminate *M. leprae* and the chronicity of the infectious response are connected with the M2 and M4 phenotypes. In addition, the presence of foamy macrophages (Mfs) with bacilli-filled vacuoles suggests that these phenotypes may prevent lipid degeneration caused by oxidative stress. The presence of M. leprae genomic DNA caused noticeable differential expression of genes implicated in type I IFN regulation, M activation, pathogen DNA detection, and recruitment of effector cells to the inflammatory site in activated MM1 genes(Quaresma et al., 2023).

TLR1, 2, and 4 markers seemed connected to serum levels of additional crucial cytokines and chemokines engaged in the development of leprosy. This information strengthens the idea that genes play a role in regulating illnesses and infections and stresses the notion that multiple genes might contribute to either susceptibility or various clinical forms of multifactorial disorders. It is still unclear, however, how this molecular network organizes a final phenotype. A great deal relies on the surroundings, and this rigorous regulation must change according to personal incentives(Santana et al., 2017).

## 5. Clinical Correlation: Spectrum of Disease and Innate Immunity

During the progression of the infectious process and defining the clinical forms of the condition, inflammatory mediators have a direct relationship with the clinical and immunopathological manifestations related with the disease. Histopathology identifies the paucibacillary (PB) kind of leprosy as tuberculoid granulomas, which are indicative of a pro-inflammatory cellular immune response. In these lesions, IL-12, IFN-γ, and TNF act on macrophages, activating phagocytosis, the generation of reactive oxygen and nitrogen reagents, and the release of the chemokine CXCL10(de Carvalho et al., 2024).

The proliferation of *M. leprae* is challenging for individuals with low cellular immune responses against the bacillus as they also have high humoral immune responses and high serum antibody levels. While TT is associated with robust cellular immunity, poor humoral immunity, and granulomatous local skin lesions, LL is characterized by robust humoral immunity(M. J. A. Silva et al., 2024).

Macrophages are activated and the formation of compact granulomas, which can restrict *M. leprae* proliferation, is promoted in TT by the predominance of Th1-type cytokines such as IFN-γ, IL-2, and TNF-α. Conversely, IL-4, IL-5, and IL-10 are the most common Th2-type cytokines in LL. This cytokine profile impairs effective macrophage activation and reduces the production of microbicidal mediators, promoting broad bacillary dissemination (Froes Junior et al., 2025).

An increase in cell-mediated immunity with CD4 and macrophage cell activation, as well as the creation of Th1-type cytokines interferon-gamma (IFN-γ), interleukin-2 (IL-2), and interleukin-12 (IL-12), are the immunopathological causes of T1R. Antigen-antibody mediated vasculitis is the immunopathology of Erythema Nodosum Leprosum (ENL)(Lockwood et al., 2011).

In the host defense against mycobacterial infections, interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) are important pro-inflammatory mediators. Both cytokines are essential for preventing the spread and dissemination of mycobacterial infections by promoting the development of granulomas that include highly differentiated, bactericidal macrophages. Numerous studies outlining the harmful effects of mutations/deletions in the TNF- and IFN-genes and their receptors on mycobacterial infection have highlighted the protective role of TNF- and IFN- Furthermore, it has been discovered that the appearance of IFN-producing cells specific to *M. leprae* protects exposed people(Lima et al., 2000). The cytokine profiles of antigen-stimulated peripheral blood mononuclear cells (PBMC) taken from individuals throughout the leprosy spectrum were investigated. Enzyme-linked immunosorbent assay (ELISA) and a reverse transcription-based polymerase chain reaction (RT-PCR) assay for mRNA cytokine transcripts were used to quantify cytokines(Misra et al., 1995). Numerous electron-dense structures that are thought to be deteriorated and fragmented M. leprae are found in the vacuolated Schwann cells and foamy macrophages of BL and LL, according to ultrastructural analyses. Sensory and motor abnormalities that result in permanent disfigurements and/or disabilities are frequently caused by peripheral nerve damage in leprosy. *M. leprae* regulated innate immune and inflammatory genes during early infection.(Pinheiro et al., 2018). *Mycobacterium spp*. may persist in a variety of environmental conditions due to humidity. At room temperature, dry nasal secretions keep bacterial cells alive for around nine days, while wet soil samples keep them alive for nearly 46 days. The chance of transmission rises in humid environments.(Alrehaili, 2023). Because they are involved in the processes that result in the emergence of the microbicidal or humoral response throughout the course of the disease, the T and B lymphocytes have essential roles in the immune response. The primary reason why this model should be reevaluated is because new cytokines have been found that alter the patterns of activation and growth of macrophages in leprosy's clinical spectrum. Future perspectives derived from this new knowledge might help to expand the immunological debate regarding the macrophage response, its differences, its importance, and the possible role of new subpopulations (M2, M4, and M17) in the immune response to *M. leprae*.(de Sousa et al., 2017).

## 6. Therapeutic and Vaccine Implications in Leprosy

Through pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and NLRs, host cells first recognize *M. leprae*. TLR2/1 heterodimers in skin macrophages are stimulated by *M. leprae*, which then encourages the eradication of *M. leprae*. Innate receptors like TLR4 can also be activated by *M. leprae*. Nevertheless, PGL-I, the most outside cell wall component of *M. leprae*, lowers the protein expression of

the TIR-domain-containing adapter-inducing interferon-β (TRIF), a TLR4 adaptor, thereby diminishing TLR4 signaling pathway activity in macrophages (Sugawara-Mikami et al., 2022).

state that PGL-I binds to particular targets, such as α-dystroglycan on Schwann cells, and interacts with the CR1, CR3, and CR4 receptors to facilitate the uptake of bacilli by macrophages, promoting myelin sheath damage and the development of nerve lesions(Froes Junior et al., 2025).

The efficacy of chemoprophylactic or detect-and-treat techniques, while providing protection against leprosy, is constrained to people who are already afflicted due to the nature of drug activity. In our opinion, leprosy control through immunization offers significant benefits over control through drug therapy for patients. The most crucial of these is that a vaccine, in contrast to medication therapy, might be utilized to provide active and sustained protection by boosting an immunological memory response. *M. bovis* BCG has been utilized to inoculate individuals as part of the most often utilized immunization plan. Although BCG is typically linked to tuberculosis, it should be mentioned that it was first created and extensively utilized to combat both tuberculosis and leprosy (Duthie et al., 2011).

The inability to grow *M. leprae* in artificial media has been the biggest challenge to developing a perfect leprosy vaccination, despite several attempts with various vaccines over the years. Three categories of leprosy vaccines exist: LepVax is a subunit vaccine, and the second category consists of cultivable mycobacteria, such as Mycobacterium indicus pranii (MIP), Mycobacterium habana, Indian Cancer Research Centre (ICRC) bacillus, BCG + M. vaccae, and BCG(Narang et al., 2024).

A good vaccine would help decrease disease incidence and encourage eradication. The native leprosy vaccine, Mycobacterium indicus pranii, has been proven to lower new cases by 60% in three years and is effective for 7–8 years before a booster dose is required to keep immunity going (Chavda et al., 2025).

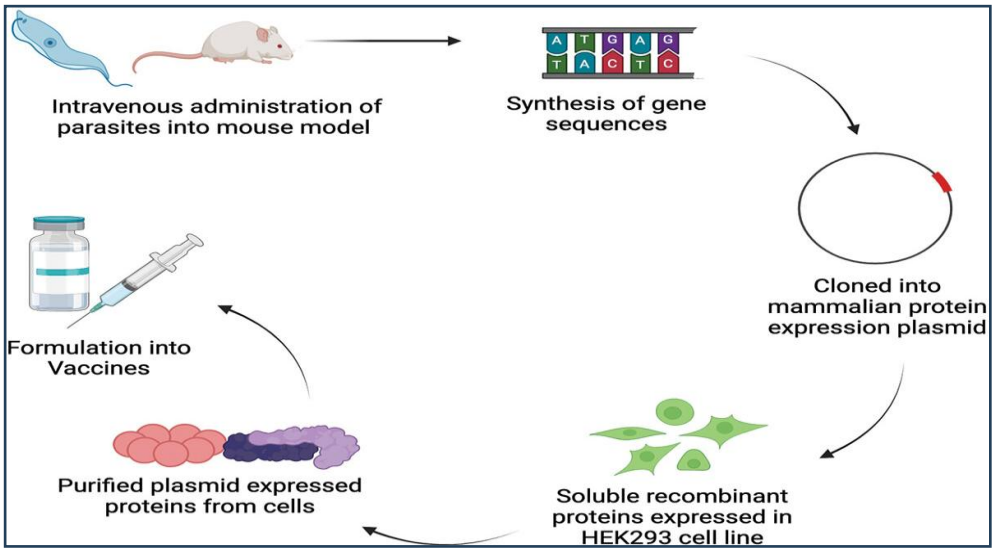

**Figure 3:** developing vaccines against infectious agents in mice(Chavda et al., 2025).

## 7. Emerging Technologies and Research Gaps

L-LEP is a disseminated and severe form of the condition that is distinguished by extensive skin damage and significant proliferation of Mlep in macrophages. Furthermore, because people are mostly the only reservoir for Mlep (, L-LEP is the main cause of infection(Mi et al., 2022).

Cells from disease lesions were subjected to single-cell RNA sequencing (scRNA-seq), which has shown to be an effective method for deconstructing granulomas' intricate multicellular structure and identifying disease-associated cell types. Typically, scRNA-seq data analysis in disease determines if a cell type is linked to a clinical form of a condition by using variations in cell type abundance. However, the genetic predisposition of the disease, which might affect the kind of host response, is seldom considered (Mi et al., 2024).

Models that incorporate new innervated (Schwann cell myelinated) and vascularized skin organoids that have been infected with *M. leprae* and co-cultured with autologous peripheral immune cells might clarify the pathophysiology of granuloma formation and immune reshaping that occur in ENL. It appears promising to construct and develop holistic skin organoids by convincing ectodermal patterning to produce co-emerging epidermal and non-epidermal lineage derivatives, neural crest cells with the capacity to give rise to mesenchymal derivatives (dermis), and Schwann cells (the preferred incubating sites for *M. leprae*) (Sharma et al., 2022).

Organoids can be generated from a variety of cell types, such as adult stem cells (ASCs), embryonic stem cells (ESCs), and iPSCs. The precise cell types and structures that develop inside the organoid may depend on the culture conditions utilized (Bombieri et al., 2024).

At their initial presentation, a considerable portion of leprosy sufferers have persistent grade 2 impairments (obvious deformities and impairments). It is known that bacillary and inflammatory cell aggregations in and around the stromal nerves of lepromatous eyes cause beading and thickening of corneal nerves, which impairs corneal feeling, encourages corneal ulceration, and eventually results in blindness (Ebenezer & Scollard, 2021).

Nerve growth factor (NGF), which was the first well-characterized neurotrophin, was notable for its regulatory roles in other neural tissues and differentiated neurons. Brain-derived neurotrophic factor (BDNF) was the second neurotrophic factor to be identified, and it shared a structural resemblance with NGF, which gave rise to the idea of the neurotrophin family. In an effort to determine the significance of

ML infection in sustaining host cell neurotrophic responses, important research on the part played by neurotrophins in leprosy have been conducted (Nogueira et al., 2020).

Diagnosis is particularly tough in pure neural varieties of leprosy because there are no cutaneous lesions and negative slit-skin smears. However, in these situations, a complete strategy that combines neurophysiological, serological, and molecular approaches—like qPCR for M. leprae DNA, anti-PGL-1 antibody identification, and electroneuromyography—has shown excellent diagnostic accuracy(Froes Junior et al., 2025).

## Conclusion

The progression factors of leprosy are linked to several interconnected complex molecular of host-parasite interaction. The early development of the host infection depends on these cells' capacity to deliver antigens and control the polarization of macrophages. Apoptosis and autophagy may be possible with differing phenotypes of the macrophages that have been attracted to the infection site, which may result in a biphasic response, i.e., allowing replication and further dissemination or its elimination. Innate immune cells try to reduce the bacterial burden by activating the adaptive immune system. The capacity of antigen presentation is actively downregulated by *M. leprae* as the bacterial load rises, which lowers the activation of T cell-mediated immunity (TT or LL form). As a result, the innate immune system plays a far larger role in the initiation of nerve damage, which is a symptom of the illness's first presentation, and in many key immunological reactions, such as inflammation and the removal of dead *M. leprae*, even while the adaptive immune system intensifies nerve damage and determines the kind of leprosy.

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